

## REMARKS

Claims 1-26 are currently before the examiner. Claims 13-15 and 24-26 have been withdrawn by the examiner as, in the examiner's view, being drawn to separate and distinct invention. Applicant traversed the withdrawal, which the examiner did not deem persuasive. Claims 1-12 and 16-23 stand rejected. Claims 1-4, 6, 11, 12, 16, and 18-21 have been amended. The amendments are made either to correct typographic errors or to more accurately describe that which the inventor considers the invention. All amendments are fully supported by the specification; no new matter has been added.

### **Objection to the specification**

The examiner has objected to the specification as containing a number of misspelled words and a number of words with letters missing and has required correction of same.

### **Applicant's response**

Applicant has amended the specification to correct all such errors that applicant could find at this time.

### **Double patenting**

The examiner has issued a non-statutory double patenting rejection of claims 16-23 over claims 1-7 of U.S. Pat. No. 5,762,957.

Applicant traverses.

### **Applicant's response**

While the examiner notes that the present claims include an "additional step" applied to the kit claimed therein and then speaks in terms of the present claims "anticipating the patented claims because the patented claims recite 'comprising' and thus opens the claims to the inclusion of additional steps," it is understood that a non-statutory terminal disclaimer requires determination of whether the challenged claims

are an obvious variation of an invention claimed in the patent. Applicant respectfully submits that they are not.

The kits of the current claims require a first compartment containing an acidic or basic buffer solution both within and outside lipid-like vesicles, wherein the vesicles are substantially impermeable to the buffer for at least one-quarter hour following loading of the chemical species and, further, the first solution has a pH selected such that the stability of the vesicle and its buffer can be maintained for a period of at least one week at 4 °C. The current claims also require a second compartment having a second solution at a selected pH wherein when the first and second solutions are mixed the resulting solution has a pH that is 0.5, 0.3 or 0.2 pH units above the pH of the buffer in the liposomes if the buffer is acidic or 0.5, 0.3 or 0.2 pH units below the pH of the buffer in the liposomes if the buffer is basic.

The patented kits, on the other hand, make no mention whatsoever as to the duration of the impermeability of its liposome membranes to the buffer or to the selection of a first solution pH so as to result in stable vesicles and buffers for at least one week. Further, the patented invention says nothing about the pH of the combined first and second solutions. Thus the patented kit requires only acids and bases and does not specify any particular pH while the current application does. The difference, i.e., from no preference to the express limitations of the current invention are not obvious.

The examiner is requested to reconsider and thereupon withdraw the terminal disclaimer over U.S. Pat. No. 5,762,957.

#### **Double patenting over U.S. Pat. No 5,827,532.**

The examiner has also issued a non-statutory double patenting rejection of claims 1-12 over claims 1-9 of U.S. Pat. No. 5,827,532.

#### **Applicant's response**

Submitted herewith is a terminal disclaimer disclaiming the term of a patent that issues from this application that exceeds the maximum permitted term of the '532 patent.

**35 U.S.C. § 112, second paragraph, rejection of claims 1-12 and 16-23**

The examiner has rejected claims 1-12 and 16-23 under § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that application regards as the invention. In particular, the examiner points out a number of errors and words missing in the claims.

**Applicant's response**

Applicant has amended the claims to, among other things, correct the scrivener's errors therein.

**35 U.S.C. § 102 rejection of claim 1**

The examiner has rejected claim 1 over § 102(b) as being anticipated by Nichols, et al., *Biochemica et Biophysica Acta*, 1976, 455:269-7. In the examiner's opinion, Nichols teaches a method of preparation of liposomes using the method set forth in claim 1. That is, as the examiner sees it, the method involved preparing liposomes with acid pH and titrating them with a base to create a pH gradient and adding a basic drug, which include epinephrine, to load the drug.

Applicant traverses.

**Applicant's response**

Claim 1 has been amended to more fully assert that which the inventor considers the invention. As such the above rejection is rendered moot. That is, Nichols is concerned only with the uptake of an amine, catechol amine, epinephrine, norepinephrine or dopamine, into an liposome using a pH gradient. Nichols does not mention, in fact clearly is not in the least concerned with, how long the amine remains in the liposome after the gradient is destroyed as clearly the case in amended claim 1 since no data or discussion of such appears in the paper.

The examiner is requested to reconsider and thereupon withdraw the rejection.

**35 U.S.C. § 102 rejection of claim 1**

The examiner has also rejected claim 1 under §102(b) as being anticipated by Deamer, et al., *Biochemica et Biophysica Acta*, **1972**, 274:323-335. In the examiner's opinion, Deamer teaches a method of preparation of liposomes using the method of claim 1. That is, the examiner notes that Deamer loads amines by preparing liposomes with acid pH and titrating them with a base to create a pH gradient and adding a basic amine.

Applicant traverses.

**Applicant's response**

As was the case with Nichols, applicants' amendment to claim 1 renders the rejection over Deamer moot. Deamer is concerned solely with the development of a probe for measuring the actual pH gradient across membranes. At no point does Deamer discuss or even allude what happens when the pH gradient is destroyed when a membrane impermeable buffer is used inside the membrane or, more specifically, to containing an absorbed chemical species within a liposome for a period of time after such destruction of the membrane.

The examiner is requested to reconsider and thereupon withdraw the rejection.

**35 U.S.C. §102 rejection of claim 1**

The examiner again rejects claim 1 under §102(b) as being anticipated by Cramer, et al., *Biochem and Biophys Research Communications*, **1977**, 75(2):295-301. In the examiner's view, Cramer teaches the method of claim 1 in it involves the preparation of liposomes and then the lowering of the pH or the external medium so as to load acidic compounds.

Applicant traverses.

**Applicant's response**

Like Nichols and Deamer, Cramer is concerned only with phenomenon of pH-induced transport of species, in this case carboxylic acids, across a liposome membrane. The only reference to elution of the encapsulated species is the statement

that "[T]he nonselective leakage of both fumaric and maleic acids depicted in Figure 4 at longer times is probably the result of vesicle rupture in response to the osmotic stress provided by the early selective transport of protonated fumaric acid." This, however, is observed while the pH gradient is still intact. There is no mention of what manner of buffer to use or to what happens to the incorporated chemical species once the gradient is destroyed as is the case in the current invention when the gradient solution is diluted under essentially pH neutral physiological conditions.

Again, the examiner is requested to reconsider and thereupon withdraw the rejection.

### **35 U.S.C. § 103 rejection of claim 1-12**

The examiner has rejected claims 1-12 as being unpatentable over Nichols or Deamer in view of Cramer. While in the examiner's view, while Nichols, Deamer and Cramer do not teach the establishment of a pH gradient by addition of an acid, the examiner deems it to be within the "skill of the art of chemistry" that if an internal medium is basic one can only establish a gradient by the addition of an acidic substance. The examiner does find that Nichols, Deamer and Cramer all teach the loading of a chemical species into a liposome using a pH gradient.

Applicant traverses.

### **Applicant's response**

Applicant does not dispute the examiner's contention that it is within the understanding of one or ordinary skill in the chemistry art that to establish a pH gradient when an internal medium is basic one should add an acid to the external medium. Applicant, however, contends that it is not within the ken of one or ordinary skill in the art to recognize that a chemical species can be maintained in the internal medium for a period of time after the loading gradient has been eliminated by using a membrane impermeable buffer. Thus, the present invention is not at all obvious.

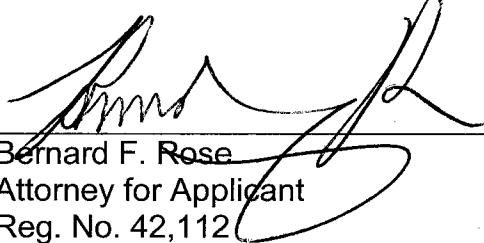
The examiner is requested to reconsider and thereupon withdraw the rejection.

**CONCLUSION**

Applicant believes that based on the amendments to the claims herein and the above Remarks, this application is in condition for allowance and respectfully requests that it be passed to issue.

In addition, applicant requests a three month extension in time within which to file this response. The Commissioner is authorized to charge the amount due to SQUIRE, SANDERS & DEMPSEY Deposit Account No. 07-1850.

Respectfully submitted,



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